Clinical translation: IVF, Endometriosis and Pregnancy Outcomes

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Overview

• Two recent studies
  – Endometriosis and unexplained infertility
    • Effect of surgical treatment
  – IVF and endometriosis
    • Unexplained IVF failure
    • Correctable defect?
  – Both studies give us insight into the role of minimal or mild disease on implantation
    • Real, profound and reversible
Implantation

- Blastocyst Stage III
- Apposition Stage IV
- Invasion Stage V
- Implantation
- Endometrium
- Morula
- 2 cell Stage II
- Fertilization Stage I
- Ovulation
- Graafian follicle
Implantation Requires Synchrony

- Wilcox et al. NEJM 340:1796, 1999
  - Delayed implantation leads to miscarriage
  - Miscarriage goes up with each day of delay
  - Clinical evidence for the window of implantation
Causes of Infertility

Diagnosis

- Unexplained: 30
- Endometriosis: 25
- Tubal factor: 15
- Ovulation: 10
- Male factor: 20
Unexplained Infertility

- 10-20% of infertile couples are given this “diagnosis”
- Reflects an incomplete infertility evaluation
- Most cases represent undiagnosed endometriosis
- Can lead to empiric and costly therapies that may be effective
Background

- ASRM supports the use of L/S in UI
- Others argue against L/S
- IVF is a cost-effective treatment
  - *Reindollar et al, FASTT Trial, FertilSteril* 2010
- IVF not covered by insurance in most states in the US
- Endometriosis reduces IVF success
  - *Barnhart et al, Fertil Steril* 2002
- IVF failures may do better after L/S
  - *Littman et al., Fertil Steril* 2005
Infertility and Endometriosis

• Evidence for this association
  – Animal models
  – Donor insemination
  – Prevalence of endometriosis in normal fertile women vs. the infertile woman
  – Progesterone resistance phenomena and DNA microarray studies
  – Treatment data (surgical, not medical)
  – IVF data (Barnhart et al)
Laparoscopy

- Required to diagnose endometriosis
- It can be therapeutic as well as diagnostic
- Useful in patients with pain or UI
What is Endometriosis?

- Fragments of the endometrium that grow outside the uterus
- Defined as the presence of glands and stroma outside the uterus
Signs of Endometriosis

- Dysmenorrhea
- Dyspareunia
- Infertility
- Late luteal spotting
- Bladder symptoms
- Bowel symptoms
- Nausea during the menses
- Nothing!
Endometriosis can be subtle or obvious
- Blue/black “Powderburn” lesions
- White - opacified
- Red flame like lesions
- Vesicular lesions
- Peritoneal windows
- Nodular (deep) endometriosis
- Adhesions/alterations in blood vessel pattern
- Invisible?
Subtle Endometriosis
Typical – with scarring
Bladder Endometriosis
Powderburn Lesions
Nodular Endometriosis
Bowel Endometriosis
Ovarian Endometriosis
Invisible Endometriosis
Inclusion Criteria

- At least 12 months of unexplained infertility
- Normal sperm count
- Open tubes
- Ovulatory, and regular cycles
- No pelvic abnormality on exam
Methods

Evaluation – Case Cohort Study

- Laparoscopy was offered to all patients
- Monitored cycles in UI patients that did or did not undergo L/S
- Video photo taken of all implants, and tissue sent to pathology for histological diagnosis
- Patients were followed for up to 12 months
- IVF pregnancies were not included in this analysis
Methods

• Kaplan-Meier Life Table Analysis was performed on each group (Graph Pad Software®)

• Stage of endometriosis was evaluated and compared by Kaplan-Meier Life Table Analysis in those that conceived (AFS Score I-II vs III-IV)
Results

• Total of 67 UI patients were identified between February 2003 and July 2010
• 57 underwent laparoscopy
• 209 monitored cycles before and 182 after L/S
• Age and BMI were similar between data sets
• Successful pregnancy was achieved in 70.1% of L/S group and 12.5% in those before laparoscopy
FIGURE 1: A – Comparison of pregnancy rates in without laparoscopy compared to treatment after laparoscopy
B – Comparison of pregnancy rates by stage of disease (I-II vs. III-IV)
Results

Figure 2A – Percent of patients with UI that had endometriosis present
Discussion

• Cause and effect on fertility controversial
  – D’Hooghe 2003

• Many women have endometriosis

• Some endometriosis is not visible or identifiable by traditional histologic methods
  – Murphy et al, *Fertil Steril* 1986

• Not all suspected endometriosis is verifiable by pathology

• A lower limit of endometriosis associated with infertility has not been defined
The “Blue” Effect
Endometriosis and IVF
Wilma

- 32 year old with UI
- Four failed fresh and 2 failed frozen IVF cycles
- No diagnosis, no pregnancy
- On laparoscopy had extensive surface endometriosis
Endometriosis and IVF Failure

• Repeated, unexplained IVF failure patients exist in most practices
  – IVF centers may not the inclination or skills to diagnose endometriosis

• Studies have suggested endometrial receptivity defects
  – (Steinleitner, 1998; Thomas et al., F&S, 2003; Littman et al., 2005; Arache et al., 2009)

• Meta-analyses suggest IVF is affected by endometriosis (Barnhart et al., F&S 2002)

• Brosens suggested aromatase expression is a marker of poor IVF performance (Brosens et al., HR, 2004)
Integrins and Implantation

- Integrins are heterodimeric glycoproteins
  - Composed of $\alpha$ and $\beta$ subunits
  - Reside in the cell membrane
  - Bind other CAMs and ECM
Presence or Absence of $\alpha v \beta 3$

- Normally present after day 20 to 21 on glandular and luminal epithelium
- Aberrant lack of $\alpha v \beta 3$ associated with endometriosis
  - Type I defects $\rightarrow$ out of phase
  - Type II defects $\rightarrow$ in phase

Lessey et al., 2000
Effect on Pregnancy in Women

- Women with endometriosis
  - Segregated by αvβ3 integrin status
  - Marked reduction in pregnancy rates in affected individuals with type II defects
  - Can be reversed with GnRH agonist
Integrin Testing

- Repeat biopsies in normal fertile controls showed consistent results.
- Integrin negative patients who underwent a second biopsy on Letrozole generally improved their integrin score.
Methods

• Integrin testing was performed prior to IVF
• Phase I – evaluate outcomes
• Phase II – prospectively determine integrin staining
• Treat integrin negative patients with aromatase inhibitor
# Medical Therapy and Infertility

<table>
<thead>
<tr>
<th>STUDY</th>
<th>MEDICAL</th>
<th>NO TREATMENT</th>
<th>PETO ODDS RATIO (95% CL)</th>
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<tbody>
<tr>
<td>Bayer</td>
<td>11/37</td>
<td>17/36</td>
<td>0.61 (0.24-1.54)</td>
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<tr>
<td>Fedele</td>
<td>17/35</td>
<td>17/36</td>
<td>1.05 (0.42-2.66)</td>
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<tr>
<td>Telimaa</td>
<td>6/18</td>
<td>6/14</td>
<td>0.67 (0.16-2.79)</td>
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<tr>
<td>Telimaa</td>
<td>7/17</td>
<td>6/14</td>
<td>0.94 (0.23-3.83)</td>
</tr>
<tr>
<td>Thomas</td>
<td>5/20</td>
<td>4/17</td>
<td>1.08 (0.24-4.78)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>48/127</strong></td>
<td><strong>50/117</strong></td>
<td><strong>0.83 (0.50-1.39)</strong></td>
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IVF Screening for $\alpha \nu \beta_3$

- In patients who completed IVF, the lack of the $\alpha \nu \beta_3$ integrin was highly predictive of failure.

<table>
<thead>
<tr>
<th></th>
<th>$\beta_3^+$</th>
<th>$\beta_3^-$</th>
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</thead>
<tbody>
<tr>
<td>Preg</td>
<td>21</td>
<td>2</td>
</tr>
<tr>
<td>Not Preg</td>
<td>14</td>
<td>33</td>
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$\chi^2$ = 25.46 $p = < 0.001$
Results

• Integrin expression was predictive of IVF success

• Addition of an aromatase inhibitor (Letrozole) on days 2 to 6 of stimulation increased IVF success
Number of Embryos Transferred

Miller et al., JSCMA 101:373-7 2005
Endometriosis and Pregnancy Loss

Minimal endometriosis

Five previous losses
Debate on how to treat

- In most states, in the USA, IVF is not covered
- The bias toward IVF for everyone discriminates against those that can’t afford the technology
- IVF doesn’t work in all patients
- Endometriosis has the potential to harm if left untreated

However...

- IVF is an efficient method to improve fertility in MOST couples
- Mild endometriosis might be an epiphenomena unrelated to the real cause of fertility
- Decisions on how to treat are often based on a belief system, rather than scientific evidence
Concluding Remarks

• Most women with UI had endometriosis at laparoscopy (L/S)

• Diagnostic accuracy was improved through the use of L/S

• Ablation and resection of all visible or barely visible endometriosis shortened time to successful pregnancy (P < 0.001)

• Just because some women are fertile with mild endometriosis, doesn’t mean everyone is
Comments

• 1) Unusual disease – paradoxical effects
• 2) Complexities –
  – Pain doesn’t correlate with disease
  – Infertility only seen in 50% of those affected
  – Medical Tx doesn’t work but surgical Tx does
• 3) Chicken and egg questions
  – Which comes first? The changing endometrium or the endometriosis
Questions to Address

1) Why are some women with endometriosis infertile while others are not?
2) How is the presence of endometriosis communicated to the endometrium?
3) If very minimal endometriosis is damaging to fertility in some women, how can we identify them?
Questions?